REMARKS

Claims 1-30 were previously pending in this application. Claims 4-6, 10-12 and 14-28 have been withdrawn from consideration as being drawn to non-elected subject matter. By this amendment, claims 1, 3, 7 and 9 have been amended and the withdrawn claims, claims 4-6, 10-12 and 14-28, have been cancelled without prejudice to the filing of an appropriate divisional/continuation application directed to the non-elected subject matter. New claims 31 and 32 have been added to claim additional embodiments of the elected invention. The number of pending claims is below the original number of claims, so no fee should be required for their entry. No new matter has been added.

In particular, Applicant has amended claims 1, 3, 7 and 9 to more clearly define and distinctly characterize Applicant's novel invention. Specifically, claims 1 and 7 were amended to recite that the polypeptide and complex, respectively, can traverse a cellular membrane. Support for these amendments can be found in the instant specification at least at paragraph [39], where Applicant teaches that polypeptides with a PTD having the amino acid sequence set forth as SEQ ID NO:1 are able to cross a cell membrane and thereby transport a cargo moiety to an intracellular location. Claims 3 and 9 were amended simply to clarify the claim language.

Applicant also has presented new claims 31 and 32 for consideration. Claim 31 is a dependent claim which clarifies that the small molecule of claim 9 can comprise a radionuclide. Support for this claim can be found at least at paragraph [53] of the instant specification and in original claim 9. Claim 32 is a dependent claim which sets forth that the cargo moiety of claim 7 is β-galactosidase or alkaline phosphatase. Support for this claim can be found at least at paragraphs [53] and [87] of the instant specification.

The amendments presented herein add no new matter and do not raise new issues requiring further search. Applicant respectfully requests entry and consideration of the foregoing amendments, which are intended to place this case in condition for allowance.

Claims 7-9 and 13 Are Definite

At page 3, section 8 of the instant Office Action, claims 7-9 and 13 stand rejected under

35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

The Office Action queries how the protein transduction domain (PTD) is "linked" to a cargo moiety in claim 7. Applicant respectfully submits that "linked" is a term of art that would be readily understood by a skilled artisan as meaning the cargo moiety is operatively attached to the PTD using an art recognized method of linking two or more molecules together. In this regard, Applicant's specification teaches methods for using a variety of suitable homo- and heterobifunctional chemical cross-linkers (specification, paragraphs [56] to [58]); methods for using bridging molecule pairs such as streptavidin and biotin, glutathione and glutathione-S-transferase, polyhistidine and an affinity chromatography reagent, and the like (specification, paragraphs [60] to [62]); and methods by which genetic fusions may be constructed (specification, paragraph [59]) in order to link a cargo moiety to a PTD. Accordingly, based on a skilled worker's professional knowledge in view of Applicant's specification, the skilled artisan would readily understand that which is claimed by the term "linked".

The Office Action further queries how, in claim 9, an atom, "radionuclide," is also a small molecule. Without acquiescing to this rejection, Applicant respectfully submits that claim 9 was amended to remove the radionuclide language. New claim 31 was added to clarify that the small molecule can comprise a radionuclide.

Thus, Applicant submits that the pending claims are definite. Accordingly, Applicant respectfully requests that this rejection of claims 7-9 and 13 under 35 U.S.C. § 112, second paragraph, as being indefinite be reconsidered and withdrawn.

The Specification Provides Adequate Written Description for Claims 1-3, 7-9, 13, 29 and 30

At page 6, section 13 of the Office Action, claims 1-3, 7-9, 13, 29 and 30 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action states that the specification describes a partial structure of the complex by disclosing the protein transduction domain as comprising SEQ ID NO:1, but that the breadth of the complex is broad because the cargo moiety can comprise any small molecule, nucleic acid and any polypeptide wherein the small molecule is selected from the group consisting of a radionuclide, a fluorescent marker, a dye and a pharmaceutical agent. The Office Action further states that although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of fusion proteins linked to cargo moieties beyond those disclosed in the examples in the specification. Applicant respectfully traverses this rejection based on the amended claims now presented.

Without acquiescing to the rejection, Applicant respectfully submits that the amended claims are directed to a polypeptide having a protein transduction domain (PTD) or a complex comprising a polypeptide having a PTD, wherein the PTD comprises the amino acid sequence set forth as SEQ ID NO:1, **and** wherein the polypeptide or complex can traverse a cellular membrane. Applicant has surprisingly discovered that the claimed PTD comprising SEQ ID NO:1 enables polypeptides having this sequence to cross cellular membranes and transport cargo moieties to intracellular compartments more efficiently than PTDs known in the art at the time of filing (specification, paragraphs [39] and [40]). Thus, the claimed polypeptide having a PTD comprising SEQ ID NO:1 and/or the claimed complex comprising a polypeptide having a PTD comprising SEQ ID NO:1 has the ***functional characteristic*** of facilitating transport across cellular membranes.

The first paragraph of 35 U.S.C. § 112 requires that the specification provide a written description of the claimed invention:

> [t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicant possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). With respect to polypeptides, the U.S. Patent and Trademark Office's Written Description Guidelines state:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by . . . disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus . . . .

66 Fed. Reg. 1099, 1106 (January 5, 2001), internal reference omitted, approved in *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325, 63 U.S.P.Q.2d (BNA) 1609, 1613 (Fed. Cir. 2002).

Applicant respectfully submits that the pending specification, particularly in view of the high level of skill possessed by workers in this technology, more than adequately describes the claimed polypeptides and claimed complexes comprising the claimed polypeptide with reasonable clarity to one of skill in the art. Applicant sets forth the amino acid sequence of a PTD comprising SEQ ID NO:1, and Applicant teaches a plethora of methods to generate the claimed polypeptides, such as by chemical synthesis, *in vitro* recombinant expression, *in vivo* expression, and cell-free expression (specification, paragraphs [42] to [47]). Further, Applicant's specification provides guidance for selecting a suitable cargo moiety for use with the claimed polypeptide (specification, paragraphs [53] and [54]) and provides guidance for attaching the cargo moiety to the claimed polypeptide (specification, paragraphs [55] to [64]). In addition,

based on Applicant's disclosure, one of ordinary skill in the art could easily determine whether the claimed polypeptide or complex could traverse a cellular membrane. Indeed, the instant specification teaches β-galactosidase and alkaline phosphatase enzymatic assays (specification, examples 1 and 8) as well as a fluorescence microscopy assay for detecting antibody binding to a cargo moiety (specification, example 7). Each of these assays could readily be used by one of skill in the art to easily quantitate PTD-mediated transduction efficiency. Thus, one of skill in the art would recognize that the specification adequately describes the claimed polypeptides and complexes.

Applicant has demonstrated that the claimed polypeptides and various complexes are capable of traversing the plasma membranes of a representative number of cells including human embryonic kidney cells, human umbilical vein endothelial cells, human dermal fibroblasts, and mouse embryonic fibroblast cells (specification, examples 1, 2, 4, 6 and 8). Applicant also teaches that complexes including either β-galactosidase or alkaline phosphatase can successfully traverse plasma membranes. *Id.* Further, at the time of filing of the subject application, other peptides/proteins were known to facilitate transport of cargo proteins across the cell membrane. In other words, the state of the art of protein transport was fairly developed. For example, a tat-derived protein transduction domain had been shown to transport either β-galactosidase or horseradish peroxidase across the plasma membrane (specification, paragraph [06]). HSV-1 VP22 was determined to be capable of transporting the 27 kDa green fluorescent protein across the plasma membrane and into the nucleus of the cell (Elliott and O'Hare (1997) *Cell* 88:223, page 229, right column, set forth as Attachment A and listed on the enclosed form PTO/SB/08a). Accordingly, in view of this evidence it is apparent that one of skill in the art, based on Applicant's teachings and the knowledge in the art at the time of filing, would readily understand that the specification sufficiently describes that the claimed polypeptides and complexes that could transduce various cargo moieties into a variety of cells.

The specification must be considered as a whole when determining whether the written description requirement is met. *In re Wright*, 866 F.2d 422, 425, 9 U.S.P.Q.2d (BNA) 1649, 1651 (Fed. Cir. 1989). The knowledge of one skilled in the art also must be considered, because the specification must "indicate[s] to persons skilled in the art that as of the [filing] date the

applicant had invented what is now claimed." *All Dental Prodx LLC v. Advantage Dental Products Inc.*, 309 F.3d 774, 779, 64 U.S.P.Q.2d (BNA) 1945, 1948 (Fed. Cir. 2002). Again, we submit that the level of skill is quite high in this technology. When read as a whole, taking into account the wealth of knowledge of persons skilled in the art at the filing date of the subject application, this specification indicates to those skilled in the art that Applicant had possession of the claimed subject matter at the time of filing. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection of claims 1-3, 7-9, 13, 29 and 30 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 1-3, 7-9, 13, 29 and 30 Are Enabled

At page 3, section 12 of the instant Office Action, claims 1-3, 7-9, 13, 29 and 30 stand rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification, while being enabling for a complex comprising a polypeptide consisting of SEQ ID NO:2 covalently linked with biotin and either an avidin conjugated β-galactosidase or avidin conjugated alkaline phosphatase that can transduce HEK 293 cells, HUVEC and NIH 3T3 fibroblast cells, does not reasonably provide enablement for any complex comprising a polypeptide consisting of SEQ ID NO:1 or SEQ ID NO:2 and any cargo moiety that can transduce any cell. The Office Action states that the claims are extremely broad in that a very large number of constituents could be encompassed by the cargo moiety, and that no limitation is placed on the utility of the complex in terms of the cell that can be transduced by the protein transduction domain. The Office Action further states that there is no way to predict whether protein transduction domain molecules will mediate the translocation of any cargo moiety into any cell. The Office Action also states that the working examples provide no guidance whatsoever in selecting other cargo moieties, which might have the needed structure for translocation across the breadth of cells encompassed by the currently claimed invention. The Office Action concludes that it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching and guidance presented. Applicant respectfully traverses this rejection based on the amended claims now presented.

35 U.S.C. § 112, first paragraph requires that the specification must enable a person

skilled in the art to make and use the claimed invention. However, a specification need not, and should not, disclose what is well known in the art. The invention that one skilled in the art must be enabled to make and use is that defined by the claims of the particular application. The issue of adequate enablement depends on whether one skilled in the art could practice the claimed invention without undue experimentation. Enablement is not precluded by the necessity of some experimentation such as routine screening, even if it is extensive routine screening. Also, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (MPEP 2164.01) if the level of skill in the art is high or if all of the methods needed to practice the claimed invention are well known. *In re Wands*, 8 U.S.P.Q. 2d 1400, 1406 (Fed. Cir. 1988).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. (Citations omitted). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 U.S.P.Q. 2d at 1404.

Applicant respectfully submits that the claims include the distinguishing features that the claimed polypeptide or complex comprising the claimed polypeptide has a PTD comprising the sequence set forth as SEQ ID NO:1, and that the polypeptide or complex comprising the polypeptide can traverse a cellular membrane. Applicant has demonstrated that the claimed polypeptides cross the cell membrane and are capable of transporting a cargo moiety to an intracellular compartment in a variety of cells. Applicant has provided ample teachings for identifying additional polypeptide and complex species using, what in this technology can only be described as, routine testing. Nothing more should be necessary to enable the claimed polypeptides and complexes for use by the highly skilled workers engaged with this technology.

Determining whether a polypeptide having the claimed PTD or complex comprising a polypeptide having the claimed PTD can traverse a cellular membrane would involve only ***routine screening***. For at least the reasons set forth above, Applicant respectfully submits that the specification teaches one of skill in the art how to make the claimed amino acid sequence, how to attach a variety of different cargo moieties to the claimed polypeptide, and how to assay

for successful traversal of the plasma membrane. Accordingly, based on these teachings, one of skill in the art could easily make and use the claimed polypeptides.

For at least the reasons set forth above, Applicant's specification, coupled with the high level of skill in the art, enables a person of skill in the art to make and/or use the claimed invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1-3, 7-9, 13, 29 and 30 under 35 U.S.C. § 112, first paragraph, as lacking enablement.

Conclusion

Having addressed all outstanding issues, Applicant respectfully requests entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

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